

WHAT IS CLAIMED IS:

1 1. A method for screening a compound to determine whether the compound
2 modulates immune cell signaling, the method comprising identifying a compound that
3 modulates interaction between a PDZ protein and a PDZ ligand protein (a PL protein),
4 wherein the PDZ protein and the PL protein are proteins which in an immune cell can interact
5 with one another to affect the composition and/or distribution of lipid rafts in the immune
6 cell.

1 2. The method of claim 1, wherein identifying comprises
2 (a) contacting a PDZ domain polypeptide that comprises at least a partial
3 sequence of the PDZ protein and a PL domain polypeptide that comprises at least a partial
4 sequence of the PL protein in the presence of the compound; and
5 (b) determining whether there is a statistically significant difference in the
6 amount of complex formed between the PDZ domain polypeptide and the PL domain
7 polypeptide in the presence of the compound as compared to the amount of the complex
8 formed in the absence of the compound, a statistically significant difference being an
9 indication that the compound is a modulator of immune cell signaling.

1 3. The method of claim 1, wherein the PDZ protein is selected from the group
2 consisting of hDlg, SHANK1, SHANK3, EBP-50, CASK, KIAA0807, TIP1, PSD-95, Pick1,
3 CNK, GRIP and DVL-2.

1 4. The method of claim 1, wherein the PL protein is selected from the group
2 consisting of PAG, LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1, fyn and Na⁺/Pi
3 transporter.

1 5. The method of claim 1, wherein
2 (a) the PDZ protein is SHANK1 or SHANK3 and the PL protein is PAG,
3 LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1 or fyn;
4 (b) the PDZ protein is TIP1 and the PL protein is LPAP or PAG;
5 (c) the PDZ protein is KIAA0807 and the PL protein is PAG or LPAP;
6 (d) the PDZ protein is EBP-50 and the PL is PAG or LPAP or BLR-1; or
7 (e) the PDZ protein is SHANK3 or EBP-50 and the PL protein is Na⁺/Pi
8 transporter.

1 6. A method for modulating immune cell signaling, the method comprising
2 modulating an interaction between a PDZ protein and a PDZ ligand protein (a PL protein),
3 which interaction affects the composition and/or distribution of lipid rafts in an immune cell;
4 and whereby such modulation alters immune cell signaling.

1 7. The method of claim 6, wherein the PDZ protein is selected from the group
2 consisting of hDlg, SHANK1, SHANK3, EBP-50, CASK, KIAA0807, TIP1, PSD-95, Pick1,
3 CNK, GRIP and DVL-2.

1 8. The method of claim 6, wherein the PL protein is selected from the group
2 consisting of PAG, LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1, fyn and Na⁺/Pi
3 transporter.

1 9. The method of claim 6, wherein
2 (a) the PDZ protein is SHANK1 or SHANK3 and the PL protein is PAG,
3 LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1 or fyn;
4 (b) the PDZ protein is TIP1 and the PL protein is LPAP or PAG;
5 (c) the PDZ protein is KIAA0807 and the PL protein is PAG or LPAP;
6 (d) the PDZ protein is EBP-50 and the PL is PAG or LPAP or BLR-1; or
7 (e) the PDZ protein is SHANK3 or EBP-50 and the PL protein is Na⁺/Pi
8 transporter.

1 10. The method of claim 6, wherein modulating comprises contacting an immune
2 cell with a compound that inhibits or enhances interaction between the PDZ protein and the
3 PL protein.

1 11. The method of claim 10, wherein the compound includes a tetrazole moiety.

1 12. The method of claim 10, wherein contacting comprises administering the
2 compound to a patient having an immune disorder, the compound being administered in an
3 amount effective to treat the immune disorder.

1 13. The method of claim 12, wherein the immune disorder is an autoimmune
2 disorder.

1 14. The method of claim 12, wherein the immune disorder is selected from the
2 group consisting of systemic lupus erythematosus (SLE), multiple sclerosis, diabetes
3 mellitus, rheumatoid arthritis, inflammatory bowel syndrome, psoriasis, scleroderma,
4 inflammatory myopathies, autoimmune hemolytic anemia, graves disease, Wiskott-Aldrich
5 syndrome, lymphoma, leukemia, severe combined immunodeficiency syndrome (SCID) and
6 acquired immunodeficiency syndrome (AIDS).

1 15. The method of claim 10, wherein the compound enhances the interaction
2 between the PDZ protein and the PL protein.

1 16. The method of claim 10, wherein the compound inhibits the interaction
2 between the PDZ protein and the PL protein.

1 17. The method of claim 16, wherein the compound is
2 (a) a polypeptide or fusion polypeptide comprising a sequence that is from
3 2 to about 20 residues of the C-terminal sequence of the PL protein;
4 (b) a polypeptide or fusion polypeptide comprising a sequence that is from
5 2 to about 100 residues of the PDZ domain of the PDZ protein; or
6 (c) a small molecule mimetic of the polypeptide or fusion polypeptide of
7 section (a) or (b).

1 18. The method of claim 6, wherein the immune cell is a T-cell.

1 19. The method of claim 6, wherein the immune cell is a B-cell.

1 20. The method of claim 6, wherein the immune cell is a monocyte/macrophage.

1 21. A modulator of binding of a PDZ protein and a PDZ ligand protein (a PL
2 protein), wherein the modulator inhibits or enhances binding of a PDZ domain polypeptide
3 and a PL domain polypeptide, and wherein

4 (a) the PDZ domain polypeptide comprises at least a partial sequence of
5 the PDZ protein and the PL domain polypeptide comprises at least a partial sequence of the
6 PL protein; and
7 (b) the PDZ protein and the PL protein are proteins which in an immune
8 cell can interact with one another to affect the composition and/or distribution of lipid rafts in
9 the immune cell.

1 22. The modulator of claim 21, wherein the modulator is formulated as a
2 pharmaceutical composition that comprises the modulator and a pharmaceutically acceptable
3 carrier.

1 23. The modulator of claim 21, wherein the modulator inhibits binding of the PDZ
2 domain polypeptide and the PL domain polypeptide.

1 24. The modulator of claim 21, wherein the modulator enhances binding of the
2 PDZ domain polypeptide and the PL domain polypeptide.

1 25. The modulator of claim 21, wherein the modulator is
2 (a) a polypeptide or fusion polypeptide comprising a sequence that is from
3 2 to about 20 residues of a C-terminal sequence of the PL protein;
4 (b) a polypeptide or fusion polypeptide comprising a sequence that is from
5 2 to about 100 residues of the PDZ domain of the PDZ protein; or
6 (c) a peptide or small molecule mimetic of the polypeptide or fusion
7 polypeptide of section (a) or (b).

1 26. The modulator of claim 21, wherein the PDZ protein is selected from the
2 group consisting of hDlg, SHANK1, SHANK3, EBP-50, CASK, KIAA0807, TIP1, PSD-95,
3 Pick1, CNK, GRIP and DVL-2.

1 27. The method of claim 21, wherein the PL protein is selected from the group
2 consisting of PAG, LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1, fyn and Na⁺/Pi
3 transporter.

1 28. The method of claim 21, wherein
2 (a) the PDZ protein is SHANK1 or SHANK3 and the PL protein is PAG,
3 LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1 or fyn;
4 (b) the PDZ protein is TIP1 and the PL protein is LPAP or PAG;
5 (c) the PDZ protein is KIAA0807 and the PL protein is PAG or LPAP;
6 (d) the PDZ protein is EBP-50 and the PL is PAG or LPAP or BLR-1; or
7 (e) the PDZ protein is SHANK3 or EBP-50 and the PL protein is Na⁺/Pi
8 transporter.

1 29. The use of a modulator of the binding of a PDZ protein and a PDZ ligand
2 protein (a PL protein) to treat an immune disorder, wherein the PDZ protein and the PL
3 protein are proteins which in an immune cell can interact with one another to affect the
4 composition and/or distribution of lipid rafts in the immune cell.

1 30. The method of claim 29, wherein the PDZ protein is selected from the group
2 consisting of hDlg, SHANK1, SHANK3, EBP-50, CASK, KIAA0807, TIP1, PSD-95, Pick1,
3 CNK, GRIP and DVL-2.

1 31. The method of claim 29, wherein the PL protein is selected from the group
2 consisting of PAG, LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1, fyn and Na⁺/Pi
3 transporter.

1 32. The method of claim 29, wherein
2 (a) the PDZ protein is SHANK1 or SHANK3 and the PL protein is PAG,
3 LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1 or fyn;
4 (b) the PDZ protein is TIP1 and the PL protein is LPAP or PAG;
5 (c) the PDZ protein is KIAA0807 and the PL protein is PAG or LPAP;
6 (d) the PDZ protein is EBP-50 and the PL is PAG or LPAP or BLR-1; or
7 (e) the PDZ protein is SHANK3 or EBP-50 and the PL protein is Na⁺/Pi
8 transporter.

1 33. The use of a modulator of the binding of a PDZ protein and a PDZ ligand
2 protein (a PL protein) in the preparation of a medicament for treatment of an immune disease,
3 wherein the PDZ protein and the PL protein are proteins which in an immune cell can interact
4 with one another to affect the composition and/or distribution of lipid rafts in the immune
5 cell.

1 34. The method of claim 33, wherein the PDZ protein is selected from the group
2 consisting of hDlg, SHANK1, SHANK3, EBP-50, CASK, KIAA0807, TIP1, PSD-95, Pick1,
3 CNK, GRIP and DVL-2.

1 35. The method of claim 33, wherein the PL protein is selected from the group
2 consisting of PAG, LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1, fyn and Na⁺/Pi
3 transporter.

1 36. The method of claim 33, wherein
2 (a) the PDZ protein is SHANK1 or SHANK3 and the PL protein is PAG,
3 LPAP, ITK, DNAM-1, Shroom, PTEN, BLR-1 or fyn;
4 (b) the PDZ protein is TIP1 and the PL protein is LPAP or PAG;
5 (c) the PDZ protein is KIAA0807 and the PL protein is PAG or LPAP;
6 (d) the PDZ protein is EBP-50 and the PL is PAG or LPAP or BLR-1; or
7 (e) the PDZ protein is SHANK3 or EBP-50 and the PL protein is Na⁺/Pi
8 transporter.